

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 February 1999 (04.02.99)	
International application No. PCT/US98/12139	Applicant's or agent's file reference UNMC 63117-A
International filing date (day/month/year) 11 June 1998 (11.06.98)	Priority date (day/month/year) 13 June 1997 (13.06.97)
Applicant KABANOV, Alexander, V. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

04 January 1999 (04.01.99)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Jean-Marie McAdams

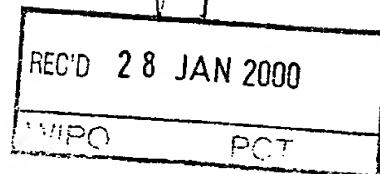
Telephone No.: (41-22) 338.83.38

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference UNMC 63117-A	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/12139	International filing date (day/month/year) 11 JUNE 1998	Priority date (day/month/year) 13 JUNE 1997
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant UNIVERSITY OF NEBRASKA BOARD OF REGENTS		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

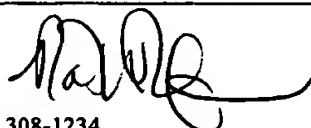
2. This REPORT consists of a total of 5 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  04 JANUARY 1999	Date of completion of this report  04 DECEMBER 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231  Facsimile No. (703) 305-3230	Authorized officer  Edward J. Webman   Telephone No. (703) 308-1234

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/12139

**I. Basis of the report**

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments).*

☒ the international application as originally filed.

☒ the description, pages 1-49 , as originally filed.

pages NONE , filed with the demand.

pages NONE , filed with the letter of \_\_\_\_\_.

pages \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

☒ the claims, Nos. 1-18 , as originally filed.

Nos. NONE , as amended under Article 19.

Nos. NONE , filed with the demand.

Nos. NONE , filed with the letter of \_\_\_\_\_.

Nos. \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

☒ the drawings, sheets/fig 1-5 , as originally filed.

sheets/fig NONE , filed with the demand.

sheets/fig NONE , filed with the letter of \_\_\_\_\_.

sheets/fig \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE .

☒ the claims, Nos. NONE .

☒ the drawings, sheets/fig NONE .

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/12139

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>1-18</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-18</u>	NO
Industrial Applicability (IA)	Claims <u>1-18</u>	YES
	Claims <u>NONE</u>	NO

**2. CITATIONS AND EXPLANATIONS**

Claims 1-18 meet the requirements of PCT Articles 33(2) and 33(4) because the prior art does not teach the claimed invention, which has industrial utility as a pharmaceutical delivery vehicle.

Claims 1-18 lack an inventive step under PCT Article 33(3) as being obvious over HUBBELL et al in view of AHMAD et al and NAKAYAMA et al.

HUBBELL et al teach block copolymers comprising a water soluble region such as polyethylene glycol and a biodegradable region such as polylactic or polyamino acid (column 7, line 6-column 8, line 68). Controlled drug delivery of active agents such as enzymes from devices such as microspheres is disclosed (column 10, lines 29-48).

AHMAD et al teach papain for aiding human digestion (abstract). Controlled release is disclosed (column 3, lines 7-11).

NAKAYAMA et al teach the stabilization of a proteolytic enzyme with a surfactant (abstract). Combinations of nonionic, anionic, and amphoteric surfactants such as hydrochloric alkylidiaminoglycine are specified (column 2, line 3 63-column 3, line 12). Papain is disclosed (column 3, lines 17-18).

It would have been obvious to one of ordinary skill to deliver papain with the device of HUBBELL et al to achieve the beneficial effect of aiding human digestion in view of AHMAD et al and to add surfactants to achieve the beneficial effect of stabilizing the enzyme in view of NAKAYAMA et al.

As to the claimed complex, is argued that such is inherently formed during mixing of the components to make the obvious composition. As to the particular claimed polyanionic and polycationic segments of the claimed block copolymer, polyaspartic acid and polylysine are well known in the art as commercially available polyamino acids for the HUBBELL et al biodegradable region. As to the particular claimed anionic and nonionic surfactants, NAKAYAMA et al disclose that the compounds recited therein are merely exemplary. Thus, NAKAYAMA et al reads on all anionic and nonionic surfactants, including those claimed. No criticality has been shown for the particular anionic and nonionic surfactants in the claims.  
(Continued on Supplemental Sheet.)

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-18 are objected to under PCT Article 6 for lack of clarity.

In claim 1, the phrase "between surfactant hydrophobic groups" is vague. On the one hand, the phrase appears to be superfluous because the surfactants are electostically bound to the polymer. On the other hand it suggests that some surfactant may not be bound to the polymer, but may be bound to the said electostatically bound surfactant molecules by hydrophobic interactions.

In claim 8, "aspartic" and "glutamic" are misspelled. In claim 15, "prostaglandins" and "leukotrienes" are misspelled.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/12139

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**CLASSIFICATION:**

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): A61K 7/075, 9/10, 47/32, 47/34, 47/36 and US Cl.: 424/ 70.11, 70.13, 70.16, 70.17, 70.22, 70.27, 486, 487, 488

**V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):**

----- NEW CITATIONS -----

US 5,410,016 A (HUBBELL et al) 25 APRIL 1995, see column 7, line 6-column 8 line 68 and column 10, lines 19-48.

US 5,531,917 A (NAKAYAMA et al) 02 JULY 1996, see abstract, column 2, line 62-column 3 line 12 and column 3, lines 17-18.

US 5,112,611 A (AHMAD et al) 12 MAY 1992, see abstract and column 3, lines 7-11.

# PATENT COOPERATION TREATY

WO 98/56334  
PCT/US98/12139

PCT

From the INTERNATIONAL BUREAU

## NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

HAGAN, Patrick, J.  
Dann, Dorfman, Herrell and Skillman  
Suite 720  
1601 Market Street  
Philadelphia, PA 19103-2307  
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 17 December 1998 (17.12.98)		
Applicant's or agent's file reference UNMC 63117-A		IMPORTANT NOTICE
International application No. PCT/US98/12139	International filing date (day/month/year) 11 June 1998 (11.06.98)	Priority date (day/month/year) 13 June 1997 (13.06.97)
Applicant UNIVERSITY OF NEBRASKA BOARD OF REGENTS et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:  
AU,BR,CA,CN,EP,IL,JP,KP,KR,PL,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:  
AL,AM,AP,AT,AZ,BA,BB,BG,BY,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,GH,GM,GW,HU,ID,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW  
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).
3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 17 December 1998 (17.12.98) under No. WO 98/56334

### REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

### REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/12139

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61K 7/075, 9/10, 47/32, 47/34, 47/36

US CL : 424/ 70.11, 70.13, 70.16, 70.17, 70.22, 70.27, 486, 487, 488

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/ 70.11, 70.13, 70.16, 70.17, 70.22, 70.27, 486, 487, 488

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,510,103 A (YOKOYAMA et al) 23 April 1996, see entire document.	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

01 SEPTEMBER 1998

Date of mailing of the international search report

13 OCT 1998

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